Upon entry of the foregoing amendment, claims 1-33 and 35-42[1] are pending in the application, with claims 1 and 17 being the independent claims. Claims 3-7, 11, 12, 15, 16, 21-27, 30-35 and 37 have been withdrawn from consideration by the Examiner. The specification has been amended to incorporate continuing application information, correct typographical errors and designate trademarks. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Claims 41 and 42 are sought to be added to the application. Support claims 41 and 42 can be found throughout the specification. In particular, support for new claims 41 and 42 can be found in the specification at page 12, lines 21-28. These claims are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejection under 35 U.S.C. § 103

The Examiner rejected claims 1, 2, 8, 13, 14, 17-20, 28, 36 and 38-40 under 35 U.S.C. § 103 as being unpatentable over U.S. Patent No. 5,166,320 (Wu *et al.*) in view of U.S. Patent No. 5,144,019 (Rossi *et al.*) and U.S. Patent No. 5,428,132 (Hirsch *et al.*). Applicants respectfully traverse the rejection.

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[1] The Examiner indicated that claim 34 is pending, but has been withdrawn from consideration. Applicants requested cancellation of claim 34 in the After-Final Amendment filed May 10, 1999. In the July 15, 1999 Office action, the Examiner stated that the Amendment filed May 16, 1999 had been entered. It is presumed that the Examiner intended the Amendment filed May 10, 1999 because Applicants did not file an Amendment on May 16, 1999 (copy of After-Final Amendment and postcard receipt attached). Clarification as to the status of claim 34 is requested.

The Examiner stated that the '320 patent teaches:

> the use of antibody-polylysine-polynucleotide conjugate for introducing polynucleotides into cells via receptor mediated endocytosis, wherein said antibody is directly coupled . . . to polylysine. The '320 patent also teaches that use of the antibody-polylysine-polynucleotide conjugate is advantageous over liposome delivery of polynucleotides because it is difficult to control the leakage of contents of the liposome and to direct cell specificity. Lastly, the '320 patent teaches that by noncovalently conjugating the polynucleotides to polylysine it allows for the polynucleotides to not be damaged or altered so successful in vivo endocytosis and expression of said polynucleotide can occur.

Office action, page 3.

The Examiner acknowledged that the claimed invention differs from the '320 patent by "the recitations of using a virus inhibiting ribozyme as the polynucleotide and monoclonal anti-CD3 antibody as the targeting ligand for T cells" (Office action, page 3).

To make-up for the deficiencies of the '320 patent, the Examiner cited the '019 and '132 patents.

According to the Examiner, the '019 patent teaches the use of a virus-inhibiting ribozyme as well as the use of a liposome for targeting the ribozyme to $CD4^+$ cells *in vivo*.

According to the Examiner, the '132 patent teaches the use of anti-CD3 monoclonal antibodies which are conjugated to DNA to deliver the DNA to T-cells *in vivo*.

The Examiner then concluded the following:

> One of ordinary skill in the art at the time the invention was made would have been motivated to use the antibody-polylysine-polynucleotide conjugate taught by the '320 patent and substitute an HIV virus inhibiting ribozyme taught by the '019 patent and monoclonal anti-CD3 antibody taught by the '132 patent because the polycation delivery method is advantageous over the liposome delivery method taught by the '019 patent because in liposomes it is difficult to control the leakage of contents of the liposome and to direct cell specificity and the use of non-covalent linkage of polynucleotides is advantageous over

> covalent linkage of DNA taught by the '132 patent because noncovalently conjugating the polynucleotides to polylysine allows for the polynucleotides to not be damaged or altered so successful in vivo endocytosis and expression of said polynucleotide can occur. Lastly the use of anti-CD3 monoclonal antibodies to target T cells would have been obvious because all HIV infected T-cells are CD3+ and specifically targeting the virus inhibiting ribozyme for cell specificity is taught by the '320 patent as use for the antibody-polylysine-polynucleotide conjugate. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Office action, page 3.

The art applied by the Examiner provides neither 1) a suggestion or motivation to combine the various references in any combination nor 2) a reasonable expectation of success of obtaining the claimed invention once the references are combined which are both necessary to establish a *prima facie* case of obviousness. *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991).

The '320 patent (Wu *et al.*) teaches a gene delivery system comprising DNA carrying complexes containing a non-covalently bound ligand conjugated to a foreign gene. This conjugate appears to be formed by binding receptor-specific ligands such as asialoglycoproteins to polycations. At column 6, lines 3-7, Wu *et al.* state that antibodies may be employed as ligands. However, Wu *et al.* make no specific reference to a targeting agent for use against cells of the T-cell lineage, as in the claimed invention. At best, there is no more than an indefinite suggestion to use any ligand, other than asialoglycoproteins. In effect, Wu *et al.'s* general statements at column 6, lines 3-7, regarding ligands result in the disclosure of a potentially infinite genus of ligands, including antibodies, although not the antibodies required for the claimed invention, i.e., those capable of binding to a cell surface protein expressed by T-cells.

As noted by the U.S. Court of Appeals for the Federal Circuit in *In re Baird,* 29 U.S.P.Q.2d 1550, 1552 (1994), a "disclosure of millions of compounds does not render obvious a claim to three compounds, particularly when that disclosure indicates a *preference* leading away from the claimed compounds" (emphasis added). Wu *et al.'s* single mention of antibodies can be said to represent a disclosure of more than "millions of compounds." Furthermore, Wu *et al.* clearly exhibit a "preference leading away from the claimed compounds" at column 6, lines 3-5, wherein Wu *et al.* recite, "*[t]ypically* glycoproteins having certain exposed terminal carbohydrate groups are used" (emphasis added). Moreover, neither the claimed protein-polycation complex nor antibodies used in the claimed complex are *sufficiently similar* in structure to any conjugate or antibody specifically disclosed in Wu *et al.* so as to render the claimed invention obvious. *See In re Jones,* 21 U.S.P.Q.2d 1941, 1943 (Fed. Cir. 1992).

The secondary references, the '019 and '132 patents, do not remedy the defects of the '320 patent.

Regarding the '019 patent (Rossi *et al.*), the patent does mention that ribozymes can be inserted into a genetic construct or used in a cell transfection system or in a therapeutic application. However, such general statements do not render the claimed invention obvious. To imply that such is the case would suggest that Rossi *et al.* render obvious virtually any use, whatsoever, of ribozymes in a therapeutic regime. This would certainly be stretching the Rossi *et al.* disclosure. Further, such general statements do not provide the motivation to combine the teachings of Rossi *et al.* with Wu *et al.* The Examiner failed to provide any evidence that the '019 patent suggests the use of ribozymes in the specific construction of polycation-protein conjugates either as claimed or as taught by Wu *et al.* Merely using ribozymes in *any* cell transfection system

is not the claimed invention. Rather a specific protein-polycation conjugate also comprising a ribozyme is necessary.

The Examiner asserted that it would have been obvious to one skilled in the art to replace the Wu *et al.* polynucleotide with the Rossi *et al.* ribozyme because the Rossi *et al.* liposome delivery method has certain disadvantages which the skilled artisan would not encounter with the Wu *et al.* delivery method, e.g., liposome leakage and the lack of cell specificity. However, it must be remembered that the motivation to combine references must be found in the prior art and not created using impermissible hindsight. Rossi *et al.* do indicate alternatives to liposome delivery. However, not one alternative listed is the Wu *et al.* conjugate or any conjugate. Thus, if one skilled in the art practicing the method of Rossi *et al.* wished to avoid liposome delivery because of, for example, liposome leakage, then the skilled artisan would employ the Rossi *et al.* liposome delivery alternatives, i.e., cellular transfection methods, such as calcium phosphate, lipofection, electroporation, or the use of a retroviral vector. *See* Rossi *et al.*, col. 6, lines 50-67. To proceed in any other manner would result in the skilled artisan proceeding contrary to the teachings of Rossi *et al.*

Moreover, there is no indication in either reference that ribozymes can be delivered to specific cells, particularly, cells of the T-cell lineage as in the claimed invention, using any conjugate.

The '132 patent (Hirsch *et al.*) teaches the use of a DNA-antibody conjugate with a direct covalent link between the DNA and the antibody. *See* column 2, lines 15-20. Particular antibodies include those against T-cells, i.e., $CD3^+$cells. Column 2, lines 52-54. The conjugates are used to integrate foreign DNA into cells. Contrary to this, the claimed conjugates are complexed to the DNA by the polycation. Thus, the Hirsch *et al.* conjugate is distinct from the

claimed conjugate. Hirsch *et al.* fail to motivate one of ordinary skill in the art to conjugate a T-cell targeting protein to a polycation and complex this conjugate with a nucleic acid. To do so, the skilled artisan would have to proceed contrary to the teachings of Hirsch *et al.* Moreover, one cannot combine Hirsch *et al.* with Wu *et al.* since, again, the skilled artisan would have to proceed contrary to the teachings of Hirsch *et al.* since the Wu *et al.* conjugates contain DNA bound to a polycation and not DNA bound to an antibody.

The Examiner asserted that it would have been obvious to one skilled in the art to substitute the Hirsch *et al.* monoclonal anti-CD3 antibody for the Wu *et al.* targeting ligand because "all HIV infected T cells are CD3+" (Office action, page 3). Further, according to the Examiner, such substitution would allow the skilled artisan to avoid the disadvantages of covalent linkage of DNA as taught by Hirsch *et al.* and exploit the advantages of non-covalent linkage of DNA as taught by Wu *et al.*

As noted above, regardless of the teachings of Hirsch *et al.*, one cannot combine Hirsch *et al.* with Wu *et al.* since the skilled artisan would have to proceed contrary to the teachings of Hirsch *et al.* The Wu *et al.* conjugates contain DNA bound to a polycation and *not* DNA bound to an antibody. Thus, even if the skilled artisan could substitute the covalent bonds of Hirsch *et al.* for the non-covalent bonds of Wu *et al.* and could substitute the Hirsch *et al.* monoclonal anti-CD3 antibody for the Wu *et al.* targeting ligand, the skilled artisan would still not arrive at the claimed conjugate or even at the Wu *et al.* conjugate. Thus, contrary to the Examiner's statement on page three of the Office action, Hirsch *et al.* do not teach a use for the antibody-polylysine-polynucleotide conjugate of Wu *et al.* or for the claimed conjugate.

The inclusion of the '019 and '132 patents in the rejection is nothing more than an attempt to add components missing from the primary reference in an attempt to arrive at the claimed

invention. Thus, overall, the Examiner has picked and chosen individual characteristics of the claimed invention from each piece of the applied art, yet has failed to provide a proper argument concerning what the motivation (as found in the cited references) might be for combining the references. By picking and choosing individual teachings of the references and then trying to put these teachings together to arrive at the claimed invention without any teaching or reasonable suggestion to do so, the Examiner is taking each of the applied references out of context. Simply because the Examiner feels that some of the individual components of the invention might be found in several different pieces of art, this does not in any way suggest the selective combination of these elements to achieve the claimed invention and is an improper approach to the obviousness analysis. Instead, the combination of references provides nothing more than an "invitation to try" numerous different possible combinations. Thus, at best, the Examiner is using an inappropriate "obvious to try" standard. *See In re O'Farrell*, 7 U.S.P.Q.2d 1673, 1681 (Fed. Cir. 1988). The motivation to combine references must be present before combining the art, not after one has already decided what they wish the combination to show.

The Examiner has failed to point out any teaching in the art which would suggest to one skilled in the art which variables are critical or which would provide guidance leading to appropriate changes necessary to obtain the claimed invention. As a result, one skilled in the art would have *no* direction concerning how to successfully obtain the claimed invention. Thus, while the cited references may recite some of the characteristics of the claimed invention, they do not suggest the selective combination of such characteristics to produce the protein-polycation conjugates that form complexes with nucleic acids and are capable of binding to a cell surface protein expressed by cells of the T-cell lineage. In other words, the likelihood of successfully obtaining the claimed invention by combining the references is extremely low especially in the

absence of any indication concerning the appropriate direction in which to proceed. As such, the applied art does not establish a *prima facie* basis for rejection under 35 U.S.C. § 103.

Applicant's position is supported in *Ex parte Obukowicz*, 27 U.S.P.Q.2d 1063 (BPAI 1992), wherein the Board reversed an Examiner's rejection under 35 U.S.C. § 103 that was based on a combination of references. In reversing the Examiner's rejection, the Board noted that, "[w]e are unable to find a suggestion [in the art] . . . *to do* what appellants have done." *Id.* at 1065 (emphasis in the original). The Board reviewed the art relied on by the Examiner and dismissed one reference stating that it was "replete with advice" but contained "little information regarding how to use the transformed bacteria and clearly does not specifically suggest appellants' use." *Id.* Applicants respectfully assert that the same could be said for the art cited in the above-captioned application. As in *Obukowicz*, none of the currently cited art is concerned with Applicants' invention, i.e., protein-polycation conjugates and nucleic acid complexes targeted to T-cells. As in *Obukowicz*, none of the art contains the specific suggestion to obtain the claimed invention, i.e., a protein-polycation conjugate comprising a protein capable of binding to a cell surface protein, other than the transferrin receptor, expressed by cells of the T-cell lineage. Further, as in *Obukowicz*, the cited art gives at best, no more than general guidance and is not *specific* as to the particular form of the claimed invention or how to achieve it.

Applicant's position is further supported by *In re Grabiak*, 226 U.S.P.Q. 870 (Fed. Cir. 1985), wherein the court held that the Examiner had not presented a *prima facie* case of obviousness because the prior art did not suggest that one of ordinary skill in the art could substitute an oxygen atom for the sulfur atom in the claimed compound. According to the court, the "mere fact that it is *possible* to find two isolated disclosures which might be combined in such a way to produce a new compound does not necessarily render such production obvious unless

the art also contains something to suggest the desirability of the proposed combination." *Id.* at 872 (emphasis in the original) (quoting *In re Bergel*, 130 U.S.P.Q. 206, 208 (CCPA 1961)).

Therefore, because the art does not suggest the particular form of the invention, and because the art does not specifically suggest that the skilled artisan do what Applicants have done, Applicants respectfully assert that no motivation exists for combining the cited art and no *prima facie* case of obviousness has been established.

Claim Objection

The Examiner objected to claims 9, 10 and 29 as being dependent upon a rejected base claim. More specifically, Applicants note, with appreciation, that the Examiner indicated that claims 9, 10 and 29 would be allowable if rewritten in independent form incorporating the limitations of the base claim and intervening claims.

Other Matters

Applicants note that the Examiner requested Applicants' assistance in correcting errors in the specification. Applicants have corrected errors in the specification of which Applicants are aware as indicated above.

Applicants request that the Examiner consider the Information Disclosure Statement filed August 28, 1996 and initial and date the form PTO-1449 that accompanied the Information Disclosure Statement. A copy of the August 28, 1996 date-stamped postcard indicating receipt of the Information Disclosure Statement, form PTO-1449 and references cited therein by the U.S.

Patent & Trademark Office, as well as a copy of the Information Disclosure Statement and form PTO-1449 are attached hereto.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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